unpatentable over **Bacus** (U.S. Patent No. 5,514,554) in view of **Rosenblum** (*Cancer Communication*, 1991) and **Hudziak** (*Molecular and Cellular Biology*, 1989). This rejection is respectfully traversed.

Bacus teaches ricin conjugated to an anti-c-erbB (anti-HER-2/neu) antibody via SPDP crosslinking. **Rosenblum** describes the conjugation of tumor necrosis factor to a monoclonal antibody against a melanoma cell specific 240 kDa glycoprotein via SPDP crosslinking. **Hudziak** reports the separate administration of unconjugated monoclonal antibody against $p185^{HER2}$/anti-erbB2 to previously sensitized breast cancer cells by unconjugated tumor necrosis factor.

Neither **Bacus** nor **Rosenblum** commented on the stability of the chemical conjugation of antibody to ricin or TNF, respectively. Regardless of the method of conjugation, however, it remains that **Bacus** pertains to an anti-erbB2/ricin conjugate while the instant invention claims a anti-erbB2/TNF conjugate. Ricin and TNF are obtained from differing natural sources with widely differing mechanisms of action. TNF acts extracellularly via

intracellular signal transduction cascades while ricin is a plant protein that inhibits protein synthesis in mammalian cells and must be internalized to cause cytotoxic efffects. Therefore, the resulting effects of substituting ricin for TNF in an antibody-toxin conjugate is not predictable without undue experimentation.

Moreover, **Bacus** states that, "importantly, it is a necessary, but not sufficient, condition that a monoclonal antibody be specific for an epitope on the extracellular domain of the HER-2/neu (erbB2) product. In other words, not all monoclonal antibodies which are able to specifically bind a region of the extracellular domain of HER-2/neu are able to induce differentiation. Some monoclonal antibodies that meet this first criterion have no effect or, worse, may have an agonistic effect on the proliferation of such malignant cells expressing HER-2/neu, such that their administration in vivo may undesirably promote growth of the malignancy. Also, a monoclonal antibody which is capable of inducing differentiation may have such an effect in one range of concentrations, but have an opposite, agonistic effect, at a different (i.e., higher or lower) concentration." (Column 6, Line 22-36). Furthermore, **Bacus'** made no mention of

the morbidity of normal cells in the course of conjugage usage. In light of **Bacus**, it is difficult to predict the efficacy of an antibody-TNF conjugate of the instant invention in lieu of the antibody-ricin conjugate of **Bacus** without undue experimentation.

On the other hand, **Rosenblum** describes an antigen from a melanoma cell line conjugated to TNF. The Examiner has previously stated that **Rosenblum** "do not teach the conjugate of tumor necrosis factor to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein." (Office Action December 22, 2000, paragraph 4). Just as it is not obvious to teach a melanoma antigen/ricin conjugate because of the diverse properties of ricin and TNF, in view of **Bacus** and **Rosenblum**, it is also not obvious to conjugate the c-erbB-2 antigen with TNF (the instant invention) due to differences in characteristics between a melanoma cell line and the carcinoma cell lines of the instant invention.

Lastly, the instant invention improves on **Hudziak** by administering TNF concurrently with the sensitizing antibody, which is more effective and specific than separate administration of TNF

and antibody. As seen from the foregoing analysis, one skilled in the art cannot predict the efficacy of tumor necrosis factor conjugated to an anti-p185^{HER2}/anti-erbB2 antibody on the target cells of the instant invention from the combination of **Bacus, Rosenblum** and **Hudziak** without undue experimentation.

Applicants thus respectfully request that the 35 USC §103(a) rejection of claims 15 and 19 as obvious over **Bacus** in view of **Rosenblum** and **Hudziak** be withdrawn.

Claims 15, 16, 17 and 19 stand rejected under 35 USC §103(a) as unpatentable over **Wels** *et al.* (U.S. Patent No. 5,571,894) in view of **Hoogenboom** *et al.* (*Biochimica et Biophysica Acta*, 4:345-354, 1991) and **Hudziak** *et al.* (*Molecular and Cellular Biology*, 1989). This rejection is respectfully traversed.

Wels *et al.* teaches the fusion of an anti-c-erbB2 single chain antibody to an effector such as a plant or bacterial toxin or drug but does not teach conjugation to tumor necrosis factor. **Hoogenboom** *et al.* teaches a single chain antibody-TNF fusion

protein but this fusion protein binds to the transferrin receptor of a myeloma cell line. **Hudziak** teaches that a monoclonal antibody against $p185^{HER2}$/anti-erbB2 sensitizes breast cancer cells to tumor necrosis factor but does not teach the conjugation of the monoclonal antibody to tumor necrosis factor.

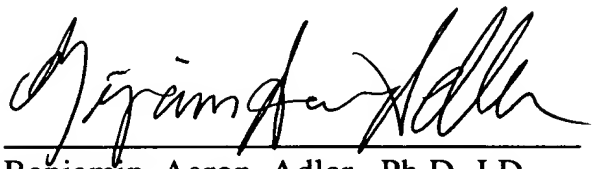
Wels teaches a toxin or drug with different action mechanisms than TNF. **Hoogenblum** involves a myeloma cell line different from the carcinoma cell lines of the instant invention. **Hudziak** does not teach conjugation of antibody to TNF. Thus, the three references in combination fail to resolve any of the uncertainties and inadequacies relative to the instant invention, namely the effectiveness of an anti-c-erbB-2-TNF conjugate against the target cells. Therefore, the Applicants respectfully request that the rejection of claims 15, 16, 17 and 19 under 35 USC §103(a) as obvious over **Wels** in view of **Hoogenboom** and **Hudziak** be withdrawn.

This is intended to be a complete response to the Office Action mailed September 13, 2001. If any issues remain

outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

DATE: Dec 31, 2001



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